



Evidence of an association between sleep and levodopa-induced dyskinesia in an animal model of Parkinson's disease



Salvatore Galati ^{a,*}, Agnese Salvadè ^a, Marta Pace ^b, Simone Sarasso ^c,
 Francesca Baracchi ^b, Claudio L. Bassetti ^{a,b}, Alain Kaelin-Lang ^{a,b}, Claudio Städler ^a,
 Paolo Stanzione ^d, Jens C. Möller ^{a,e}

^a Experimental Laboratory, Neurocenter of Southern Switzerland, Lugano, Switzerland

^b Department of Neurology, University of Berne, Berne, Switzerland

^c Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, Milan, Italy

^d Department of Neurology, University of Rome "Tor Vergata", Rome, Italy

^e Parkinson Center, Center for Neurological Rehabilitation, Zihlschlacht, Switzerland

ARTICLE INFO

Article history:

Received 27 July 2014

Received in revised form 1 November 2014

Accepted 15 December 2014

Available online 23 December 2014

Keywords:

Parkinson's disease

Levodopa-induced dyskinesia

Sleep

Synaptic homeostasis

Slow-wave activity

ABSTRACT

Levodopa-induced dyskinesia (LID) represents a major challenge for clinicians treating patients affected by Parkinson's disease (PD). Although levodopa is the most effective treatment for PD, the remodeling effects induced by disease progression and the pharmacologic treatment itself cause a narrowing of the therapeutic window because of the development of LID. Although animal models of PD provide strong evidence that striatal plasticity underlies the development of dyskinetic movements, the pathogenesis of LID is not entirely understood. In recent years, slow homeostatic adjustment of intrinsic excitability occurring during sleep has been considered fundamental for network stabilization by gradually modifying plasticity thresholds. So far, how sleep affects on LID has not been investigated. Therefore, we measured synaptic downscaling across sleep episodes in a parkinsonian animal model showing dyskinetic movements similar to LID. Our electrophysiological, molecular, and behavioral results are consistent with an impaired synaptic homeostasis during sleep in animals showing dyskinesia. Accordingly, sleep deprivation causes an anticipation and worsening of LID supporting a link between sleep and the development of LID.

© 2015 Elsevier Inc. All rights reserved.

1. Introduction

Levodopa (LD)–induced dyskinesia (LID) is difficult to treat, negatively affects quality of life, and increases the treatment costs of Parkinson's disease (PD) patients (Dodel et al., 2001). Although LD currently represents the most effective treatment for PD patients (Poewe et al., 2010), ameliorating cardinal signs such as bradykinesia, akinesia and rigidity (Katzenschlager and Lees, 2002), these benefits are in some measure overshadowed by the emergence of LID (Jankovic and Stacy, 2007). In the early stages, PD patients usually experience an acceptable quality of life that is impaired in the advanced stages by the emergence of these involuntary movements that frequently occur at the peak of the LD effect

(Berthet and Bezard, 2009; Nadjar et al., 2009). In other words, when the patients experience motor complications such as a shortening motor response and the development of dyskinesia, the delivery of LD without inducing dyskinesia becomes increasingly difficult (Jankovic and Stacy, 2007; Olanow et al., 2006).

Several attempts have been made to find "pure" anti-dyskinetic drugs, able to uncouple the anti-akinetic effect from the dyskinetic one of LD and other dopamine (DA) agonists. As a consequence, great efforts have been made to clarify LID pathogenesis, emphasizing the role of pulsative stimulation of striatal receptors by dopaminergic treatment (Olanow et al., 2006), and also changes of postsynaptic (Calabresi et al., 2010; Jenner, 2008) or presynaptic processes at the striatal level (Lunardi et al., 2009). Although no conclusive results on LID pathogenesis have been achieved, disease duration, that is, the degree of dopaminergic degeneration, along with long-term use of LD, seems to play a crucial role (Berthet and Bezard, 2009; Nadjar et al., 2009). This is perceivable in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced parkinsonism in humans in whom the extended dopaminergic damage caused

* Corresponding author at: Department of Neurology, Neurocenter of Southern Switzerland, Via Tesserete 46, Lugano 6903, Switzerland. Tel.: +41 (0)91 8116921; fax: +41 (0)91 8116915.

E-mail address: salvatore.galati@eoc.ch (S. Galati).

within a few days of LD treatment the development of LID undistinguishable from those in the idiopathic form (Langston and Ballard, 1984). Promising results with respect to LID pathogenesis come from animal models and PD patients demonstrating an uncontrolled long-term potentiation (LTP) of corticostriatal synapses in association with the development of LID (Calabresi et al., 2000; Picconi et al., 2003). Striatal medium spiny neurons of dyskinetic rats have an impaired reversal of the previously induced LTP, that is, “depotentialization” (Picconi et al., 2003). Furthermore, PD patients showing LID were unresponsive to the depotentialization paradigm suggesting that depotentialization is abnormal in the motor cortex of patients with LID (Huang et al., 2011). Dyskinetic movements can be interpreted as intruding motor programs in selected neuronal responses because of unrestrained LTP. Physiological control of spike-timing-dependent plasticity (STDP) such as LTP has a crucial role in network stability (Turrigiano and Nelson, 2004). Recently, an important role for sleep and in particular for electroencephalographic (EEG) slow-wave activity (SWA) has been proposed. According to the concept of synaptic homeostasis (SH) hypothesis, SWA is believed to underlie an overnight homeostatic process, by which neuronal circuit activity is not driven toward runaway excitation by LTP (Tononi and Cirelli, 2014). Moreover, SWA spectral density analysis represents a reliable measure of synaptic downscaling during nonrapid eye movement (NREM) sleep (Tononi and Cirelli, 2014; Vyazovskiy et al., 2007) and recent compelling evidence associated SWA to cortical synaptic strength and therefore measuring the reduction in SWA from early (the first 1 hour at the beginning of the light period) to late (the last 1 hour of the light period) NREM sleep has often been used as a direct measure of SH (Vyazovskiy et al., 2007).

STDP and homeostatic plasticity involve, in different ways, the trafficking of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) by different calcium dynamics. Some signaling molecules are linked to postsynaptic expression of AMPARs, and among these, the Arc protein seems to be a critical mediator of this cellular phenomenon (Béïque et al., 2011). A physiological decrease in Arc has been demonstrated during sleep (Hanlon et al., 2009), and an increased level of the Arc protein has been shown in the striatum of dyskinetic rats (Sgambato-Faure et al., 2005).

Indeed, sleep disturbances are frequently associated with PD, often preceding the motor onset of the disease itself and revealing the intimate role of DA in regulating the sleep-wake cycle (Dzirasa et al., 2006). Furthermore, improvement of motor performance in the morning is frequently mentioned by patients, principally in those with a long history of the disease and motor fluctuations (Bateman et al., 1999). Parallel to the disease progression, a progressive change in the physiological sleep architecture is observed, which includes a significant decrease in the amount of NREM sleep (Diederich et al., 2005; Rye and Jankovic, 2002).

In the present article, we investigated whether the development of LID might be associated with a critical impairment of synaptic downscaling during NREM, implying sustained retention of aberrant synaptic memories within the corticobasal ganglia-thalamic loop. To examine our hypothesis, we measured the synaptic strength in the following 5 animal groups: (i) sham-lesioned drug-naïve rats (sham/LD⁻), (ii) sham-lesioned LD-treated rats (sham/LD⁺), (iii) 6-hydroxydopamine (6-OHDA)-lesioned drug-naïve rats (PD/LD⁻), (iv) 6-OHDA-lesioned LD-treated rats without dyskinesia (PD/DYS⁻), and (v) 6-OHDA-lesioned LD-treated rats with dyskinesia (PD/DYS⁺). We found that PD/DYS⁻ animals had a physiological sleep-induced reduction of synaptic strength, whereas PD/DYS⁺ animals do not manifest an adequate reduction in SWA, thus possibly implying reduced synaptic downscaling during sleep. Concordantly,

behavioral experiments demonstrated that sleep deprivation (SD) was able to enhance the emergence of LID during LD treatment (Cam et al., 2013).

2. Methods

2.1. Animals

Experimental procedures were carried out on 142 adult male Sprague-Dawley rats (Harlan, Udine, Italy) weighing 170–200 g corresponding to ~6 weeks of age (Table 1, Fig. 1A and B). The study was conducted in compliance with Swiss laws on animal experimentation and the National Institute of Health's *Guide for the Care and Use of Laboratory Animals*. All procedures were performed minimizing animal discomfort and strain. Rats were maintained on a regular light-dark cycle (lights on at 10:00 AM, lights off at 10:00 PM; room temperature 20–22 °C; and maximum 3 animals per cage) and were given food (Harlan RM Diet; Harlan) and water ad libitum before habituation to the behavioral paradigm. The study design and the experimental groups are depicted in Fig. 1A. We employed a 6-OHDA-based parkinsonian rat model inducing abnormal involuntary movements (AIMs) comparable with LID observed in PD patients by chronic treatment with LD. The experimental procedures were conducted in the following 5 animal groups: (i) sham/LD⁻, (ii) sham/LD⁺, (iii) PD/LD⁻, (iv) PD/DYS⁻, and (v) PD/DYS⁺. Electrophysiological and molecular experiments were performed in a blind manner in relation to assignment to the previously mentioned experimental groups.

2.2. Unilateral 6-OHDA-lesion model of PD

Unilateral (left hemisphere) DA denervation was performed according to a standard protocol (Galati et al., 2008; Schwarting and Huston, 1996). Briefly, rats were anaesthetized with 1.5%–2.5% isoflurane in oxygen and mounted on a stereotaxic instrument (Stoelting Co, Wood Dale, IL, USA). Body temperature was maintained at 37–38 °C with a heating pad (Stoelting Co) placed beneath the animal. After a subcutaneous injection of the local anesthetic bupivacaine, a midline scalp incision was made, and a hole (\emptyset of ~1.0 mm) was drilled in the skull on the left side. The neurotoxin (30-mM solution of 6-OHDA containing 0.03% of ascorbic acid) was injected into the medial forebrain bundle (coordinates: 4.0 mm posterior of the bregma, 1.3 mm laterally of the midline, and 7.0 mm beneath the cortical surface). Injections of 3 μ L of 6-OHDA were administered through a 30-gauge cannula connected to a 10- μ L Hamilton syringe over a period of 3 minutes. The injection of neurotoxin was preceded by a bolus of desipramine (25 mg/kg, intraperitoneally) to minimize the uptake of 6-OHDA by noradrenergic neurons. Two weeks later, an apomorphine-induced rotation test (0.05 mg/kg, subcutaneously) was performed to assess the severity of nigral lesions (Galati et al., 2008; Hudson et al., 1993). Animals performing at least 100 rotations opposite to the lesion site within 20 minutes from the apomorphine treatment (Hudson et al., 1993) were considered successfully lesioned and included in the study (Fig. 1B).

2.3. Induction of dyskinesia by chronic LD treatment

For the induction of LID, 6-OHDA-treated animals were submitted to LD treatment as described elsewhere (Fig. 1B and Cenci et al., 1998). Briefly, the rats were subcutaneously treated for 3 weeks with LD methyl ester (Sigma-Aldrich) at a daily dose of 8 mg/kg in combination with 15-mg/kg benserazide (Sigma-Aldrich). LID was rated 20 minutes after the injection according to a dyskinesia rating scale (Cenci et al., 1998). The rats were

Download English Version:

<https://daneshyari.com/en/article/6804721>

Download Persian Version:

<https://daneshyari.com/article/6804721>

[Daneshyari.com](https://daneshyari.com)